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Molecular/Clinical Correlations in Females With Fragile X

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Females who are affected by fragile X syndrome (FXS) can have significant physical, neuropsychological and emotional involvement. This study was designed to explore the relationships between these three domains and to learn how the degree of involvement in each of these phenotypic areas relates to molecular parameters including CGG repeat length and activation ratio (the proportion of normal FMR1 alleles on the active X chromosome). Three groups of females were studied: 35 women who grew up in a fragile X family but do not carry an FMR1 mutation, 92 women with a premutation, and 29 women with a full mutation. Correlations between neurocognitive, physical and emotional traits were calculated for each of the three groups. Within the full mutation group significant correlations were seen between schizotypal traits and full scale IQ. The Lie scale was significantly correlated with the physical findings index. The activation ratio correlated significantly with the measure of executive function ($r = .50$, $P = .01$). There was a trend toward correlations of activation ratio with the physical index score, outer ear prominence and IQ. CGG repeat number significantly correlated only with the physical index ($r = .44$, $P = .01$). Thus, activation ratio may be the more pertinent molecular parameter in full mutation women in determining the degree of cognitive and physical phenotypic involvement.

KEY WORDS: fragile X females, schizotypy, neurocognitive deficits, physical findings, CGG repeats, X-inactivation ratio

INTRODUCTION

A broad spectrum of involvement exists in females who are carriers of the FMR1 mutation. Females with a premutation demonstrate normal cognitive abilities [Reiss et al., 1993; Mazzocco et al., 1993; Rousseau et al., 1991a, 1994] whereas approximately 50% of females with a full mutation demonstrate some degree of cognitive deficit [Rousseau et al., 1994; Loesch and Sampson, 1993; Hagerman et al., 1992]. Our previous work has identified traits within three phenotypic domains, physical, emotional and neurocognitive, which are particularly sensitive to the effects of the FMR1 mutation in females. In Hull and Hagerman [1993], the physical index score (PI) and the anthropometric measures of inner and outer ear prominence[1] detected differences between controls and females with a full mutation. Additionally, differences were detected between females with a premutation and controls. In Sobesky et al. [1992, 1994a,b] the findings of schizotypal traits and a high Lie scale from the MMPI-2 characterized females with a full mutation compared to controls. In Mazzocco et al. [1992, 1993], the findings of frontal or executive function deficits characterized females with a full mutation compared to controls and this effect remained even when the influence of overall IQ was statistically controlled. It has been postulated that the schizotypal traits are related to the neurocognitive deficits, specifically the frontal or executive function deficits, reported in females with a full mutation [Mazzocco et al., 1993].

Molecular correlates of cognitive involvement in the full mutation range have been studied by Taylor et al. [1994] and Abrams et al. [1994]. The activation ratio (the proportion of cells with the normal FMR1 gene on the active X chromosome) was determined in both studies by Southern blot analysis and band quantitation described by Rousseau et al. [1991b]. The Taylor et al. [1994] study did not find a significant correlation between IQ and CGG length or activation ratio (AR) within the full mutation range in females. Abrams et al. [1994], on the other hand, found a significant cor-

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[1] Inner ear prominence is measured from the side of the head at right angles to the inner aspect of the pinna. Outer ear prominence is measured from the side of the head at right angles to the outer aspect of the top of the pinna.

relation between cognitive measures and both AR and CGG repeat length. The AR had a more robust effect than repeat length and both correlated with different cognitive subtests suggesting to these authors an independent effect on cognitive measures.

The present study was undertaken to understand the relationship among the physical, neurocognitive and emotional domains and the influence of the molecular parameters, CGG amplification and activation ratio, in each domain.

MATERIALS AND METHODS

Subjects were volunteers for an ongoing study of fragile X syndrome (FXS) in adult women. They were recruited through the Child Development Unit at The Children's Hospital in Denver, Colorado. Women ranged in age from 18 to 45 and all achieved an IQ of 70 or greater on the Wechsler Adult Intelligence Scale-Revised [Wechsler, 1981]. Subjects were paid for their participation. All signed consent forms and this research was approved by the research review committee at The Children's Hospital. Participants were assigned to one of three groups according to the results of DNA testing: Group 1: Controls (n = 35) without a FMR1 mutation who grew up in a home where a parent and, for most, a sib has a FMR1 mutation; Group 2: Subjects (n = 92) who demonstrate a premutation on PCR or Southern blot analysis (50–200 CGG repeats); Group 3: Subjects (n = 29) who demonstrate a full mutation (greater than 200 CGG repeats) by Southern blot analysis. Participants in the subject groups were assigned on the basis of DNA analyses including OX1.9 or STB 12.3 probes [Taylor et al., 1994] and PCR using the method described by Pergolizzi et al. [1992]. Expansions beyond 200 are considered to be more clinically significant than premutations because they are associated with gene dysfunction through hyper-methylation and transcriptional silencing of the mutant FMR-1 gene [Fu et al., 1991; Pieretti et al., 1991]. The CGG repeat length utilized for this study was the lowest band size detected in the full mutation range. The methodology for detecting the activation ratio by evaluating Southern blot band density patterns was described by Rousseau et al. [1991b] and previously utilized by Taylor et al. [1994]. Activation ratio was determined for 21 of the 29 individuals (74%) in the full mutation group.

All participants were administered a neurocognitive battery containing a measure of general intellectual ability, the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [Wechsler, 1981] and measures of neuropsychological functioning including executive functions described below. Examiners were blind as to the cytogenetic and DNA results of the subjects. Full-scale IQ scores were generated for all subjects based on the WAIS-R.

Two measures considered sensitive to executive functions (functions thought to be monitored by the frontal lobes) formed the executive function composite score: the Contingency Naming Test (CNT) and the Wisconsin Card Sorting Task (WCST). The CNT, developed by Taylor [1988], consists of an array of 27 shapes (triangles, circles, and squares) varying in color (blue, pink, or green) that are presented together on a piece of paper. The subject is required to name each design according to one of four rules, presented in order of increasing difficulty. Each rule dictates whether the stimulus should be referred to by its color or its shape. Similar to a Stroop task, this test is used to measure one's ability to inhibit a highly probable but unrequested response, as well as one's ability to shift response set. The WCST procedure as standardized by Heaton [1981] also measures set-shifting ability. In a factor analysis of a broad battery of executive function measures given to a separate large (N = 145) sample, the CNT and the WCST loaded on the same "set-shifting" factor as the Stroop; other executive function measures loaded on either an "inhibition" or "verbal working memory" factor [Pennington, in press]. It is acknowledged that important issues remain regarding the definition, reliability, and validity of executive function measures [Pennington, in press; Pennington et al., 1996].

Scores for the executive functions domain were created by first generating z-scores for each test. To create z-scores, we used the mean and standard deviation of the entire sample (Groups 1, 2 and 3 combined). For each subject, the two z-scores were added together to create a composite score. Finally, these composite scores were restandardized by generating a new z-score (EF) based on the entire sample. The use of z-scores allowed us to put scores on a common metric.

The same women completed the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) [Hathaway and McKinley, 1989]. The MMPI-2 consists of 567 items which are rated as true or false by subjects. MMPI-2 scores were generated via computer scoring for the Lie (L), a measure of the tendency to portray one's self in an unrealistically positive manner.

Data about schizotypal traits were derived using a structured interview, the Structured Interview for Schizotypy (SIS) developed by Kendler et al. [1989]. The SIS consists of 19 sections. Eighteen assess various social and cognitive behaviors associated with schizotypy. The final section required the interviewer to rate the respondent based on their behavior during the SIS and other, less structured parts of the interview. Subjects were administered the SIS by another examiner who was blind to subjects' DNA results.

SIS scores were transformed into dimensions of Schizotypal Personality Disorder based on DSM III-R [American Psychiatric Association, 1987]. [For a more detailed description of the scoring see Sobesky et al., 1994a]. Previous analyses indicated that women carrying a full mutation differed from women carrying a premutation and from controls on three of the nine DSM III-R criteria for Schizotypal Personality Disorder: oddness, tangential thinking, and lability/constriction of affect. A schizotypal scale was constructed by summing the positive scales across three dimensions. The range of the schizotypal scale was 0 to 3.

Each patient also underwent a physical examination including the measurement of ear prominence using a sliding caliper and a subjective evaluation of ten landmarks which make up the Physical Index (PI): long face, long ears (≥7.0 cm), prominent ears, high arched

palate, flat feet, hyperextensible finger joints (≥90 degree extension of the metacarpal phalangeal joints), double jointed thumbs, heart murmur or click, Sidney or Simian palmar crease, and hand calluses. The findings were then added to calculate a PI score between 0 and 10 with 1 point for each trait present [Hull and Hagerman, 1993; Cronister et al., 1991]. The exact measure of outer-ear circumference was also utilized as this has been shown to differentiate full mutation and premutation carrier women from controls [Hull and Hagerman, 1993].

Anovas were used to test for significant DNA group differences for the six clinical variables of interest. Pearson correlation coefficients were used to investigate relationships between the variables. It was expected that relationships between physical and emotional variables would be positive (i.e., more physical signs would be associated with more emotional signs). It was also expected that relationships between neurocognitive, emotional and physical variables would be negative (i.e., the better the neurocognitive functioning, the fewer physical signs or emotional symptoms). Within the full mutation group, it was expected that there would be no significant relationships between CGG repeat size and the various clinical traits. It was expected that activation ratio would be positively associated with neurocognitive variables and negatively associated with physical and emotional variables. Because the direction of relationship was predicted a priori, one-tailed tests of significance were used. Given the large number of correlations, a p level of .01 or less was adopted for a single correlation to be considered statistically significant. However, correlations significant at the .05 level or less and consistent with a priori hypotheses are reported as well. All analyses were done utilizing the SPSS statistical computer package [Norusis, 1990].

RESULTS

Group means for each of the six variables of interest (Lie scale, schizotypal traits, outer ear prominence, physical index, executive function score and full scale IQ) were compared using one-way analyses of variance. As can be seen in Table I, there was a significant effect for DNA group for each of the variables; in all cases full mutation carrier women were significantly different from premutation carrier women and control women. Full mutation carrier women displayed higher Lie scores, more schizotypal traits, larger outer ear prominence, higher physical index scores, lower full scale IQ and lower executive function skills than premutation women or controls. These group differences remained significant when additional analyses, controlling for the effects of IQ, socioeconomic status, and age, were performed. Table I also contains the percentage of women in each group who were a standard deviation or more above or below the mean of the control group for each of the variables.

Also of interest was the relationship between the emotional, physical and neurocognitive variables, and their relationship to CGG repeat length and activation ratio as a function of DNA group. Table II presents all of these Pearson correlation coefficients. As would be expected, full scale IQ and executive function skills are

TABLE I. Means and Standard Deviations of Emotional, Physical, and Neurocognitive Variables by DNA Group†

Variables	Group (n)	Mean	Standard deviation	Percentage problems[a]
Lie*	1 (34)	52.65	9.83	14%
	2 (88)	53.73	9.37	17%
	3 (28)	66.93	14.06	52%
Scz**	1 (35)	0.20	.47	17%
	2 (92)	0.51	.91	29%
	3 (29)	1.38	1.21	66%
Ear***	1 (31)	1.52	.30	3%
	2 (88)	1.58	.39	19%
	3 (29)	1.90	.39	41%
PI****	1 (33)	1.09	1.10	11%
	2 (89)	1.58	1.30	19%
	3 (29)	3.00	1.79	59%
IQ*****	1 (35)	106.26	12.17	11%
	2 (92)	104.96	12.81	9%
	3 (29)	82.59	9.59	69%
EF******	1 (35)	.36	.76	3%
	2 (92)	.28	.70	4%
	3 (29)	−1.59	.99	90%

† Groups: 1 = Control women; 2 = Premutation women; 3 = Full Mutation women. Variables: L = Lie Scale from MMPI-2; Scz = Schizotypal Features scale; Ear = Outer Ear Prominence; PI = Physical Features Index; IQ = Full Scale IQ; EF = Executive Functions z-score.
[a] Percentage of subjects with scores greater (Lie, Scz, Ear, PI) or less (IQ, EF) than one standard deviation from the mean of the control group (group 1).
* $F(2, 147) = 19.02$, $P < .0001$. Group 3 > Groups 1, 2.
** $F(2, 153) = 14.84$, $P < .0001$. Group 3 > Groups 1, 2.
*** $F(2, 145) = 9.77$, $P = .0001$. Group 3 > Groups 1, 2.
**** $F(2, 148) = 16.63$, $P < .0001$. Group 3 > Groups 1, 2.
***** $F(2, 153) = 18.29$, $P < .0001$. Group 3 < Groups 1, 2.
****** $F(2, 153) = 70.81$, $P < .0001$. Group 3 < Groups 1, 2.

significantly correlated in each group, although the correlation in full mutation carriers ($r = .71$, $P < .001$) is higher than that within the other two groups ($r = .48$, $P < .01$ for controls and $r = .40$, $P < .001$ for premutation women). Within the control group, executive function skills are negatively correlated with the Lie scale ($r = -.44$, $P < .01$), as are schizotypal manifestations ($r = -.32$, $P < .05$).

In premutation carrier women, IQ is negatively correlated with the Lie scale ($r = -.27$, $P < .01$). Outer ear prominence is positively correlated with the Lie scale ($r = .21$, $P < .05$) and with schizotypal traits ($r = .18$, $P < .05$). The CGG repeat number and the Activation Ratio did not correlate with any phenotypic findings in the premutation group.

In the full mutation group, schizotypal traits are negatively correlated with IQ ($r = -.50$, $P < .01$) and executive functions ($r = -.33$, $P < .05$), and positively correlated with the physical index ($r = .31$, $P < .05$) as predicted. The Lie scale is positively correlated with schizotypal traits ($r = .40$, $P < .05$) and the physical index ($r = .48$, $P < .05$) and negatively correlated with IQ ($r = -.35$, $P < .05$) as predicted. As expected, the physical index is negatively correlated with IQ ($r = -.41$, $P < .05$).

Within the full mutation group, CGG repeat size is positively correlated with the physical index score only ($r = .44$, $P < .01$). The activation ratio is positively correlated with executive functions ($r = .50$, $P < .01$) and negatively with outer ear prominence ($r = -.40$, $P < .05$). There is a trend toward significance in the cor-

TABLE II. Correlations of Emotional, Physical, Neurocognitive, and Genetic Variables by DNA Group†

Variables	Group	L	Scz	Ear	PI	IQ	EF	CGG	AR
L	1	—	−.32*	−.09	.13	−.15	−.44**	—	—
	2	—	.09	.21*	−.06	−.27**	−.15	.08	—
	3	—	.40*	.11	.48**	−.35*	−.14	.15	.14
Scz	1	—	—	−.00	.08	.02	−.06	—	—
	2	—	—	.18*	.12	.01	−.07	.06	—
	3	—	—	−.31*	.31*	−.50**	−.33*	.01	−.11
Ear	1	—	—	—	.15	−.28	.04	—	—
	2	—	—	—	.34***	−.04	−.10	.09	—
	3	—	—	—	.19	−.04	.06	.01	−.40*
PI	1	—	—	—	—	−.09	−.06	—	—
	2	—	—	—	—	.06	.06	−.03	—
	3	—	—	—	—	−.41*	−.21	.44**	−.33
IQ	1	—	—	—	—	—	.48**	—	—
	2	—	—	—	—	—	.40***	−.14	—
	3	—	—	—	—	—	.71***	−.02	.33
EF	1	—	—	—	—	—	—	—	—
	2	—	—	—	—	—	—	−.05	—
	3	—	—	—	—	—	—	.01	.50**
CGG	1	—	—	—	—	—	—	—	—
	2	—	—	—	—	—	—	—	—
	3	—	—	—	—	—	—	—	.08

† Groups: 1 = Control women; 2 = Premutation women; 3 = Full Mutation women. Variables: L = Lie Scale from MMPI-2; Scz = Schizotypal Features scale; Ear = Outer Ear Prominence; PI = Physical Features Index; IQ = Full Scale IQ; EF = Executive Functions z-score; CGG = CGG repeat length; AR = Activation Ratio.
* $P < .05$.
** $P < .01$.
*** $P < .001$, one-tailed significance tests.

relations of activation ratio with the physical index ($r = -.33$, $P = .07$) and with IQ ($r = .33$, $P = .07$). Therefore the Activation Ratio is the most robust of the two molecular parameters probably because it will have the greatest impact on levels of FMRP.

We had earlier hypothesized that (1) the physical phenotype was the most sensitive to the fragile X mutation, based on the finding of outer ear prominence in some premutation females [Hull and Hagerman, 1993]; and that (2) executive function (EF) deficits underlie schizotypal traits and elevated Lie scale scores. The CGG repeat number correlated only with the Physical Index score so this phenotypic measure appears to be the most sensitive to the effects of a higher CGG repeat number. The second hypothesis is not strongly supported by the correlations discussed above.

Another test of both these hypotheses is to examine whether different phenotypic changes occur in an orderly sequence within subjects. If there is an orderly sequence of involvement, then there should be few or no subjects with aspects of the behavioral phenotype who do not have physical abnormalities. Likewise, if the executive function deficits are causal to the emotional phenotype, then there should be few or no subjects with elevations in Lie scale or schizotypal traits without EF deficits. We scored each relevant physical or behavioral anomaly as present or absent in premutation and full mutation groups based on a one SD cutoff using control data, and then tested for the predicted sequences.

In the premutation group, 36 women had aspects of the behavioral phenotype but none of the physical phenotype, whereas only 5 had the reverse pattern. Similarly in the full mutation group, 9 women had aspects of the behavioral phenotype, but none of the physical phenotype; none had the reverse pattern. We can clearly reject the hypothesis that the phenotypic involvement occurs in an orderly sequence with the physical changes always displayed first.

With regard to the hypothesis that the EF deficits are causal to the emotional phenotype, we found that in the premutation group, 23 women had aspects of the emotional phenotype (Lie or schizotypal) but no EF deficit, whereas 10 showed the reverse pattern. In the full mutation group, we cannot adequately test the hypothesis because the rate of EF deficits (26 of 29 subjects) is very high, so there is little opportunity for someone to have emotional deficits without EF deficits. Three women did, whereas 11 had the reverse pattern (in addition, 15 women had both and none had neither). Therefore, across both the premutation and full mutation groups we do not find clear support for the hypothesis that EF deficits are causal to the emotional phenotype.

DISCUSSION

In the full mutation group, emotional variables were negatively correlated with neurocognitive variables (i.e., the higher the full scale IQ or more executive function skills, the lower the Lie scale and fewer schizotypal symptoms), as expected. Emotional variables were positively correlated with the physical index (i.e., the more physical symptoms, the higher the Lie scale and the more schizotypal anomalies) but not with the other physical measure, outer ear prominence. One physical measure, the physical index was negatively correlated with IQ as predicted; but there were no significant cor-

relations between outer ear prominence and either of the neurocognitive measures in the group of women with a full mutation.

In the premutation group, outer ear size, but not the physical index was positively correlated with the Lie scale and schizotypal traits (i.e., the greater the ear prominence, the higher the Lie scale and the more schizotypal findings). Also, the Lie scale was negatively correlated with IQ. In the control group, the Lie scale was negatively correlated with executive function skills, as would be expected. But the Lie scale was also negatively correlated with schizotypal traits, a direction opposite to the one found in full mutation women. This suggests a unique relationship between the Lie scale and schizotypal aspects in fragile X syndrome compared to controls. Both the high Lie scale and schizotypal traits are associated with involvement from fragile X syndrome and they both correlate with a lower IQ in women with a full mutation.

Caution must be taken in interpreting these correlations. As noted earlier, a large number of correlations was calculated and many of those reported are significant at the .05 level or less and not at the .01 level. Thus, there is the possibility that some may be due to chance. However, we have reported them because they were consistent with our a priori hypotheses which suggests that they may not be spurious. Clearly, these results need to be replicated with larger sample sizes.

The relation among phenotypic domains apparently is not sequential (physical first and behavioral second) or causal (EF deficits are necessary for these aspects of the emotional phenotype). Instead each phenotypic domain appears to be substantially but not completely independent of the others. There are many other genes besides FMR1 that will affect manifestations in each phenotypic domain. The highest r^2 we found between phenotypic domains is less than .25, so most of the variance in a phenotypic domain is not predictable from variance in another. The hypothesis that best fits this pattern of results is one of pleiotropy. The fragile X mutation acts somewhat separately on each of these phenotypic domains. However, there are important relationships among the domains that may influence the severity in the domains. For instance, the presence of EF deficits may worsen the severity of schizotypal traits. Measures of FMRP will allow us to test this hypothesis of pleiotropy more rigorously.

No relationships were found between repeat length and variables within the premutation group. Therefore the CGG repeat length does not predict the subgroup of women with the premutation who may be mildly affected as has been suggested in males with a high CGG repeat number in the premutation range [Hagerman et al., 1996]. In the full mutation women, there was a positive relationship between the physical index and the CGG repeat length. Also, in the full mutation group, there was a positive relationship between activation ratio and executive function skills (i.e., the greater the percentage of normal X chromosomes activated, the higher the executive function skills) and a negative relationship between the AR and outer ear prominence (i.e., the more active normal X chromosomes, the smaller the outer ear prominence). The trends for a negative relationship between PI and AR and a positive relationship between IQ and AR were also in the predicted directions. The correlation between AR and EF and outer ear prominence suggest that activation ratio is the best molecular measure at this time to predict degree of involvement for full mutation fragile X women.

For a full mutation (which is hypermethylated and therefore does not produce FMRP), it is unclear why CGG repeat number would correlate with phenotypic measures. Perhaps full mutations with fewer CGG repeat numbers have a tendency to be unmethylated in a proportion of cells in some tissues or to produce FMRP particularly in the 200 to 350 ranges as shown by Feng et al., 1995. None of the full mutation carrier females studied have had evidence of incomplete methylation in the blood.

The correlation between outer ear size and schizotypal traits within the premutation group suggests a subgroup of premutation women who may have effects from the mutation. Perhaps this is related to occult expansion of the premutation in other tissues or a deficit in FMRP in those with the premutation as has been reported in a small number of males [Hagerman et al., 1996]. Further study of this subgroup of women with the premutation will help us to understand the reason for mild phenotypic involvement.

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